Remarks

Reconsideration of this Application is respectfully requested.

Upon entry of the foregoing amendment, claims 2 and 6-8 are pending in the application, with 2 being the independent claim. Claim 2 has been amended. Support for the amendment can be found in the specification at page 10, lines 12-21 and page 20, lines 15-28. These changes are believed to introduce no new matter, and their entry is respectfully requested.

Based on the above amendment and the following remarks, Applicants respectfully request that the Examiner reconsider all outstanding objections and rejections and that they be withdrawn.

Rejections Under Obviousness-Type Double Patening

Claims 2 and 6-8 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1 and 3 of U.S. Patent No. 6,183,974. Applicants respectfully traverse this ground of rejection.

The Examiner alleges that the instant claims are entirely encompassed by the claimed subject matter in the aforementioned patent. The issue is not whether the claims of the U.S. Patent No. 6,183,974 (the '974 Patent) are encompassed by the current claims, but rather whether the current claims are obvious in view of the claims of the '974 Patent. Such is not the case. Claim 2 in the current application recites "a method

for determining whether a compound of interest affects an adenylyl cyclase ***or phospholipase C pathway*** and therefore is an agonist or antagonist of a receptor which couples to ***both*** Gs and Gq proteins...."

In view of the claims of U.S. Patent No, 6,183,974, the claims of the current application are non-obvious given the additional recitation of "adenylyl cyclase" and "Gs proteins." This addition further focuses the method to identify compounds which not only couple to Gq proteins, via the phospholipase C pathway, but which couple Gs proteins as well. The method encompasses receptors which are dual signaling molecules, as distinguished from purely Gq coupled receptors. This further limitation is non-obvious given that the claims of the '974 Patent make no mention of receptors that could couple both Gs and Gq proteins. Thus, Applicants respectfully request that the Examiner reconsider and withdraw this rejection.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 2 and 6-8 are rejected under 35 U.S.C. § 112, second paragraph as being indefinite, for failing to distinctly claim the subject matter which applicants regard as the invention. Specifically, the Examiner states that the claim is "vague and indefinite because there is no clear antecedent basis...." Applicants respectfully traverse this rejection.

Solely in an effort to expedite prosecution, and without acquiescence in the propriety of the rejection, Applicants have amended claim 2, from which claims 6-8

depend, to recite "a method for determining whether a compound of interest affects ***an*** adenylyl cyclase or phospholipase C pathway." Thus, the rejection is moot.

Rejections under 35 U.S.C. § 112, Second Paragraph

Claims 2 and 6-8 are also rejected under 35 U.S.C. § 112, second paragraph for allegedly being incomplete. Applicants respectfully traverse this ground of rejection.

More specifically, the Examiner states that "clearly some additional step or steps are required to permit an artisan to distinguish between a compound which effects either of these two pathways directly or through a mechanism other than a heterologous receptor and a compound which effects either of these pathways indirectly by activating or inhibiting the heterologous receptor of interest." Applicants disagree.

The Examiner appears to be requesting that Applicants distinguish between different mechanisms by which the invention may work. This is not a requirement under 35 U.S.C. § 112, second paragraph or any other section of the code of which Applicants are aware. Applicants have set forth the scope of the invention as required under 35 U.S.C. § 112, second paragraph and therefore the claim is not indefinite. Nowhere has the Examiner set forth any recitation in the claim that would not be readily understood by one of skill in the art.

In the event that the Examiner actually meant to reject the claims under 35 U.S.C. § 112, first paragraph the following overcomes such a rejection. The claimed invention recites a method of determining whether a compound affects "either an adenylyl cyclase pathway or phospholipase C pathway and therefore is an agonist or antagonist of a receptor which couples to both Gs and Gq proteins...." One of skill in the art practicing

the invention would be able to establish whether a receptor transfected into a cell line, which normally does not express said receptor, was responsible for an effect on the adenylyl cyclase or phospholipase C pathways through routine experimentation involved in practicing Applicants' invention.

In any event, in an effort to expedite prosecution, Applicants have amended claim 2 to describe a basis by which the activity of u-PA may be assayed in the cell culture supernatant. From the activity of the u-PA, the skilled artisan would be able to distinguish between compounds that are agonist or antagonists of the stated pathways as taught in the specification (Pg. 20, lines 15-28 and Pg. 10, line 12-21). Thus, the rejection has been overcome, or is moot, and Applicants respectfully request that the Examiner withdraw the objection.

Rejections under 35 U.S.C. § 101

Claims 2 and 6-8 have been rejected under 35 U.S.C. § 101 because the disclosed invention is allegedly inoperative and therefore lacks utility. Applicants respectfully traverse this ground of rejection.

The Examiner argues that the invention is inoperative due to the rejection under 35 U.S.C. § 112, second paragraph as being inoperative. However, in light of the previously described amendment of claim 2 this rejection is now moot.

Rejections under 35 U.S.C. § 103(a)

Claims 2 and 6-8 have been rejected as being unpatentable over Catanzariti, *et al.*, *BioTechniques 15*(3):474-479 (1993) ("Catanzariti") in view of the combination of U.S. Patent No. 5,494,806 to Segre *et al.* ("Segre") and the Bringhurst *et al.*, *Endocrinology 132*:2090-2098 (1993) publication ("Bringhurst"). Applicants respectfully traverse this ground of rejection.

To establish a *prima facie* case of obviousness under 35 U.S.C. § 103, the Examiner must show that the prior art suggested the modification of the reference or references required to arrive at the claimed invention, and that the invention could be attained with a reasonable expectation of success. See *In re Vaeck*, 20 U.S.P.Q.2d 1438, 1442 (Fed. Cir. 1992). Any suggestion and reasonable expectation of success must come from the prior art of record, and not Applicants' disclosure *Id.*

Nothing in Catanzariti teaches or suggests Applicants' method for screening compounds which are agonists or antagonists of receptors to both Gs and Gq proteins. In fact, Catanzariti is entirely focused on the use of the u-PA response in LLC-PK1 cells to detect responses mediated by receptors coupled to ***only*** Gs.

Segre does not cure the deficiencies of Catanzariti. Segre may mention expressing human PTH/PTHRP receptor in LLC-PK1 cells. However, Segre does not suggest that the PTH receptor is a dual-signaling receptor. This is significant because the assay of the present invention describes measuring the u-PA activity to determine whether a compound is an agonist or antagonist of a dual-signaling receptor (the PTH

receptor). By "dual signaling" it is meant a receptor which couples to both Gs and Gq proteins and whose activation may be measured by u-PA activity.

Bringhurst does not cure the deficiencies of Segre or Catanzariti. The Examiner states that Bringhurst teaches the functional expression of a recombinant mammalian PTH/PTHRP receptor like the human PTH/PTHRP receptor of Segre in LLC-PK1 cells prior to the time of the instant invention. However, the Bringhurst assay system only indicates whether a compound is an agonist or antagonist of a Gs-coupled receptor. In Bringhurst, there is no teaching of whether PTHR stimulation by an agonist or antagonist of a Gs and Gq coupled receptor could be detected by an increase in u-PA activity.

None of the references cited by the Examiner provide suggestion or provide motivation to transfect LLC-PK1 cells with a G protein coupled receptor for the purpose of determining whether a compound of interest is an agonist or antagonist of a receptor which couples to both Gs and Gq proteins. The Examiner states that:

> "Because an artisan of ordinary skill in the art of molecular biology was well aware that the ultimate value of the information obtained from an assay like that which was described by Catanzariti et al. would lie in the applicability of that information to human subjects that artisan would have found it *prima facie* obvious to have transfected DNA encoding the human PTH/PTHRP receptor of Segre et al. into the LLC-PK1 cells of Catanzariti et al., to permit the pharmacological characterization of that receptor. Because the Bringhurst et al. publication had shown that LLC-PK1 cells could be stably transformed with a DNA encoding a mammalian PTH/PTHRP receptor and that this receptor couples to the adenylate cyclase system of those cells, an artisan had more than reasonable expectation that a DNA encoding the human PTH/PTHRP receptor of Segre et al. could be functionally and stably expressed in the LLC-PKC1 cells of Catanzariti et al. and their activity assayed by measuring urokinase-type plasminogen activator as taught therein."

However, no skilled artisan could have known that the PTH/PTHRP receptor, expressed in LLC-PK1 cells not only couples to the adenylate cyclase system but that the same receptor also signals through the phospholipase C pathway and both of these responses

can independently augment u-PA activity. No skilled artisan could have know this because this information was discovered by the inventors. Therefore, the rejection has been overcome and should be withdrawn.

Conclusion

All of the stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections and that they be withdrawn. Applicants believe that a full and complete reply has been made to the outstanding Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone the undersigned at the number provided.

Prompt and favorable consideration of this Amendment and Reply is respectfully requested.

Respectfully submitted,

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Version with markings to show changes made

Claim 2 was amended as follows:

2. (twice amended) A method for determining whether a compound of interest affects [either the] an adenylyl cyclase or phospholipase C pathway[s] and therefore is an agonist or antagonist of a receptor which couples to both Gs and Gq proteins comprising:

(a) providing a cell line which expresses urokinase-type plasminogen activator (u-PA);

(b) providing an expression vector comprising a nucleotide sequence encoding for a receptor which couples to both Gs and Gq proteins, said receptor not normally expressed in said cell line of step (a);

(c) introducing said expression vector into said cell line, thereby providing stably transfected cells;

(d) contacting said stably transfected cells;

and

(e) measuring the u-PA activity of the cell culture supernatant of said cells of step (d) by fluorescence or absorbency spectroscopy, thereby determining whether said compound of interest is an agonist or antagonist of a receptor which couples to Gq and Gs proteins.